IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	KUMAR *et al.*	Atty. Dkt. No.:	RLL-330US
Serial No.:	10/541140	Group Art Unit:	Unknown
Filing Date:	June 30, 2005	Examiner:	Unknown

Title: MAGNESIUM SALT OF IMIDAZOLE DERIVATIVE

Certificate of Mailing

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Kim Campbell

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Commissioner of Patents
Alexandria, VA 22313-1450

TRANSMISSION OF PRIORITY DOCUMENT

Applicants transmit herewith a certified copy of Indian Patent Application No. 20/Del/2003 filed 7 January 2003 (7.01.2003) to which priority is claimed herein.

Respectfully submitted,

RANBAXY LABORATORIES LIMITED

By: William Hare
William D. Hare
Senior Counsel – Intellectual Property

Dated: July 26, 2005
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सत्यमेव जयते

INTELLECTUAL PROPERTY **INDIA**

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

BEST AVAILABLE COPY

CERTIFIED COPY OF PRIORITY DOCUMENT

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.* ***20/Del/2003 dated 7th January 2003.***

Witness my hand this 17th day of January 2005.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

- 7 JAN 2003

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5 (2), 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"MAGNESIUM SALT OF IMIDAZOLE DERIVATIVE"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. further declare that the inventors for the said invention are

a. YATENDRA KUMAR

b. MOHAN PRASAD

c. NEELA PRAVEEN KUMAR

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representative of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 2343126, 2342001 – 10; 8912501-10
Fax No. (91-124) 2342027

6. Following declaration was given by the inventors in the convention country:

We, YATENDRA KUMAR, MOHAN PRASAD, NEELA PRAVEEN KUMAR of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a.

(YATENDRA KUMAR)

b.

(MOHAN PRASAD)

c.

(NEELA PRAVEEN KUMAR)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **686503** dated : **18.12.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **6TH** day of **January, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

FORM 2 00220 DEL 03

- 7 JAN 2003

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

MAGNESIUM SALT OF IMIDAZOLE DERIVATIVE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a novel magnesium salt of rabeprazole, to processes for preparing it, pharmaceutical compositions of the salt and to its use in treatment or prevention of gastrointestinal ulcers.

Background of the invention

US 5045552 discloses several substituted pyridylmethylsulfinyl benzimidazoles, including 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methylsulfinyl]-1*H*-benzimidazole i.e. rabeprazole. Rabeprazole is a proton pump inhibitor and an antibacterial agent. Rabeprazole sodium is used for treating and preventing peptic ulcers, and for treating bacterial infections caused by camphylobacter and helicobacter pylori.

While the patent mentions that some of the disclosed compounds can form a salt with metals such as sodium, potassium, calcium or magnesium, only sodium salts of the disclosed compounds have been prepared. In particular, only the sodium salt of rabeprazole has been synthesized besides rabeprazole freebase. Also, the commercial product of rabeprazole (Aciphex by Eisai Inc.) uses rabeprazole sodium. Rabeprazole sodium is obtained in amorphous form by the process described in this patent, and is hygroscopic in nature.

A recent Japanese Patent Application JP 2001039975 describes nonhygroscopic crystals of benzimidazolyl pyridylmethyl sulfoxides, including rabeprazole sodium, and their preparation.

Summary of the invention

The present invention relates to magnesium salts of rabeprazole i.e. rabeprazole magnesium. A preferred form of rabeprazole magnesium is rabeprazole hemimagnesium. Another aspect of the invention relates to rabeprazole magnesium in an amorphous form.

The invention also relates to a process for preparing rabeprazole magnesium, which comprises contacting rabeprazole freebase or its sodium salt with magnesium salt of an acid in a suitable solvent to form rabeprazole magnesium, wherein the process is carried out in the presence of a base whenever rabeprazole freebase is used.

The invention further provides an alternative process for preparing rabeprazole

magnesium, which comprises reacting rabeprazole freebase with magnesium alkoxide in an alcohol as solvent to form rabeprazole magnesium.

Further aspects of the invention include a method for treating or preventing gastrointestinal ulcers which comprises administering to a patient in need thereof an effective amount of rabeprazole magnesium, and a pharmaceutical composition for use in the treatment or prevention of gastrointestinal ulcers that comprises an effective amount of rabeprazole magnesium along with pharmaceutically acceptable excipients.

Detailed description

The term "rabeprazole magnesium" as used herein means any salt comprised of rabeprazole anions and magnesium cations. For instance, solid as well as dissolved forms are included as are crystalline and amorphous forms.

Further, the term "rabeprazole magnesium" encompasses stoichiometric as well as non-stoichiometric ratios of rabeprazole anion and magnesium cation. The ratio of rabeprazole to magnesium is not required to be 1:1 in order to be termed rabeprazole magnesium. Rabeprazole magnesium is preferably formed as a salt having a 2:1 molar ratio between rabeprazole anion and magnesium cation (i.e., rabeprazole hemimagnesium). Rabeprazole hemimagnesium may be formed even when an excess of rabeprazole or an excess of magnesium salt of an acid is used in the salt formation.

Rabeprazole magnesium obtained in an amorphous forms is non hygroscopic. Amorphous form may be advantageous in comparison with the crystalline form as it is obtained in a finely powdered form with better solubility properties.

Rabeprazole magnesium and particularly rabeprazole hemimagnesium may exist in an anhydrous and/or solvent-free form or as a hydrate and/or a solvate. The hydrates of rabeprazole magnesium, especially hydrates of rabeprazole hemimagnesium form another aspect of the invention.

Further, rabeprazole magnesium can exist as one of two enantiomers due to the presence of a chiral center. The enantiomers may either be separated e.g., by subjecting rabeprazole freebase or the sodium salt to resolution using an optical purity embedding agent (CN 1223262, see Chem. Abs. 133:17460) and converted to the corresponding

magnesium salt, or prepared by stereo selective oxidation of the corresponding sulfide in the presence of a chiral titanium complex and a base (US 5948789), and converted to the corresponding magnesium salt The individual enantiomers as well as mixtures thereof are likewise all embraced by the singular expression "rabeprazole magnesium."

Rabeprazole magnesium can be prepared by a process which comprises contacting rabeprazole freebase or its sodium salt, with magnesium salt of an acid in a suitable solvent, preferably with both the magnesium salt of an acid and rabeprazole freebase or its sodium salt being fully dissolved therein.

Whenever rabeprazole freebase is used, the process is carried out in the presence of a base. Suitable bases which may be used in the process along with rabeprazole freebase include alkali metal hydroxides such as sodium hydroxide or potassium hydroxide, alkali metal carbonates such as sodium carbonate or potassium carbonate, and alkali metal bicarbonates such as sodium bicarbonate.

Magnesium salt of an acid to be used in the process can be the salt of any inorganic or organic acid such as, magnesium chloride, magnesium nitrate, magnesium sulphate, magnesium phosphate, magnesium carbonate, magnesium dihydrogenphosphate, magnesium oxalate, magnesium acetate, magnesium lactate, magnesium succinate, magnesium citrate, and magnesium tartrate.

Suitable solvents for carrying out the process include water, alcohols such as methanol, ethanol or isopropanol, ketones such as acetone or methyl isobutyl ketone, esters such as ethyl acetate, ethers such as dioxan or tetrahydrofuran, nitriles such as acetonitrile, dipolar aprotic solvents such as dimethylsulfoxide or dimethylformamide, hydrocarbons such as hexane or toluene and mixtures thereof.

Water is the preferred solvent as the reactants are more soluble than the rabeprazole magnesium product. In this way, the salt forming reaction is accompanied by spontaneous precipitation of the produced magnesium salt out of the solution. The above described methods allow for the production of rabeprazole magnesium in an amorphous form.

Alternatively, the precipitation may be facilitated by reducing the volume of the solution and/or by adding an antisolvent, i.e. a solvent in which the rabeprazole magnesium is

insoluble or sparingly soluble. The precipitation can also be induced by reducing the temperature of the solvent, especially if the initial temperature at contact is elevated. Crystalline or partially crystalline material may sometimes be obtained by such processes.

Rabeprazole magnesium can be prepared by an alternative process, which comprises reacting rabeprazole freebase with magnesium alkoxide in an alcohol as solvent to form rabeprazole magnesium. Commercially available Magnesium alkoxide may be used, or it may be generated in situ by refluxing magnesium metal (turnings or ribbon) in the corresponding alcohol, which also acts as the solvent.

Suitable alkoxides which may be used in the process include magnesium methoxide, magnesium ethoxide, magnesium propoxide and magnesium isopropoxide. Suitable alcohols include methanol, ethanol, propanol and isopropanol.

The rabeprazole freebase or its sodium salt to be used in the preparation processes can be obtained by methods known in the art including those described in the above mentioned patent, as well as in US 6313303, WO 01/04109, WO 02/062786 and WO 02/083608.

Generally, the rabeprazole magnesium is precipitated out of the solution or reaction mixture. The precipitation may be facilitated by reducing the volume of the solution and/or by adding an antisolvent, i.e. a solvent in which the rabeprazole magnesium is insoluble or sparingly soluble. The precipitation can also be induced by reducing the temperature of the solvent, especially if the initial temperature at contact is elevated.

The precipitated magnesium salt may be isolated in a solid state by conventional methods such as filtration or centrifugation, optionally followed by washing and/or drying and may be purified by crystallization.

Rabeprazole magnesium is a useful proton pump inhibitor and an antibacterial, and thus can be used to treat any condition that would be benefited by administration of a gastric acid secretion inhibitor. In particular, rabeprazole magnesium can be used for healing of erosive or ulcerative gastroesophageal reflux disease (GERD); maintenance of healing of erosive or ulcerative GERD; healing of duodenal ulcer; treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome, by administering an

effective amount of the salt to a patient in need thereof. The specific form of rabeprazole magnesium to be used is not particularly limited and specifically includes rabeprazole hemimagnesium.

The salt can be administered by any suitable route including oral, parenteral or transdermal. The "patients" intended to be treated include human and non-human mammals.

The salt is usually administered as part of a pharmaceutical composition. Accordingly, a further aspect of the invention is a pharmaceutical composition for treating or preventing gastrointestinal ulcers that comprises an effective amount of rabeprazole magnesium and pharmaceutically acceptable excipients. The salt may be conveniently formulated into tablets, suspensions, injectables and other pharmaceutical forms.

In the following section preferred embodiments are described by way of examples to illustrate the process of the invention. However, these are not intended in any way to limit the scope of the present invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.

EXAMPLE 1

2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methylsulfinyl]-1*H*-benzimidazole, hemimagnesium salt

Magnesium turnings(1.0g, 0.004m) were refluxed in methanol (100ml) with a spec of iodine for two hours. The above solution was cooled to 20°C and rabeprazole base (25 g, 0.0696 m) was added. The mixture was stirred for 15 minutes and the solution filtered to remove the undissolved matter. The filtrate was concentrated under reduced pressure. The residue was stirred in ethyl acetate (100ml) for 30 minutes. The solid obtained was filtered, washed with ethyl acetate and dried at 40°C under vacuum to give rabeprazole magnesium (21.9g).

Assay (by HPLC) : 98.8%, Water (w/w) : 6.88%, Mg content (w/w) : 2.96%

^{1}H- HMR ($CDCl_3$, δ, ppm); 2.03-2.04(m, 5H), 3.33(s, 3H), 3.48-3.52(t, 2H), 4.02 (t, 2H), 4.72(bs, 2H), 6.63(bs, 1H), 7.25(d, 2H), 7.57(m, 2H), 8.22(d, 1H).

XRD, IR and DSC spectra are as shown in Figure I II, & III respectively.

EXAMPLE 2

2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methylsulfinyl]-1*H*-benzimidazole, hemimagnesium salt

Rabeprazole sodium (10g, 0.0262 m) was dissolved in methanol (175ml) at room temperature. Magnesium acetate (2.8g, 0.013m) was added to the above solution. The solution was stirred for 1 hour at room temperature, and then filtered to remove the undissolved particles. The filtrate was concentrated under reduced pressure. The residue. was stirred in diisopropyl ether 30 minutes, the solid obtained was filtered, and dried. It was then suspended in water (50ml), stirred for 30 minutes, filtered, washed with water and dried at 40°C under vacuum to give 8.5g of white partially crystalline rabeprazole magnesium. Water (w/w) : 6.11%.

EXAMPLE 3

2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methylsulfinyl]-1*H*-benzimidazole, hemimagnesium salt

Rabeprazole sodium (10g, 0.0262m) was dissolved in water (75ml) at room temperature. Magnesium acetate (2.8g, 0.013m) dissolved in water (25ml) was slowly added to the above solution in 30 minutes. Rabeprazole magnesium precipitated out simultaneously. The suspension was further stirred for 30 minutes, the obtained solid was filtered and washed with water. The product was dried at 40°C under reduced pressure to give rabeprazole magnesium (8.8g).

Water (w/w) : 5.8%; XRD, IR and DSC spectra are similar to those for example 1.

EXAMPLE 4

2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methylsulfinyl]-1*H*-benzimidazole, hemimagnesium salt

Sodium hydroxide flakes (1.1g, 0.027m) were dissolved in water (80ml). To the above solution was added rabeprazole base (10 g, 0.027 m) at 10-15°C and stirred till a clear solution was obtained. Magnesium acetate (3.0g, 0.027m) dissolved in water (20ml) was added to the resulting solution. The reaction mixture was stirred for 30 minutes. The solid that separated out was filtered, washed with water and dried under vacuum at 40°C to give rabeprazole magnesium (8.8g).

Water (w/w) : 5.46%; XRD, IR and DSC spectra are similar to those for example 1.

WE CLAIM:

1. A magnesium salt of rabeprazole.

2. The salt according to claim 1, which is rabeprazole hemimagnesium.

3. The salt according to claim 1 or 2, which is in hydrated.

4. The salt according to claim 1 or 2, which is in amorphous form.

5. A process for preparing rabeprazole magnesium, which comprises contacting rabeprazole freebase or its sodium salt with magnesium salt of an acid in a suitable solvent, to form rabeprazole magnesium, wherein the process is carried out in the presence of a base whenever rabeprazole freebase is used.

6. The process according to claim 5, wherein the magnesium salt of an inorganic acid is used.

7. The process according to claim 6, wherein the magnesium salt is selected from the group consisting of magnesium chloride, magnesium nitrate, magnesium sulphate, magnesium phosphate, magnesium carbonate, and magnesium dihydrogenphosphate.

8. The process according to claim 5, wherein the magnesium salt of an organic acid is used.

9. The process according to claim 8, wherein the magnesium salt is selected from the group consisting of magnesium oxalate, magnesium acetate, magnesium lactate, magnesium succinate, magnesium citrate, and magnesium tartrate.

10. The process according to claim 5, wherein the base is selected from the group consisting of alkali metal hydroxides, alkali metal carbonates, and alkali metal bicarbonates.

11. The process according to claim 10, wherein the base is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, and sodium bicarbonate.

12. The process according to claims 5, wherein the solvent is selected from the group consisting of water, alcohol, ketone, ester, ether, nitrile, dipolar aprotic solvent, hydrocarbon and mixtures thereof.

13. The process according to claim 12, wherein the solvent is selected from the group consisting of methanol, ethanol, propanol, acetone, methyl isobutyl ketone, ethylacetate, dioxan, tetrahydrofuran, acetonitrile, dimethylsulfoxide, dimethylformamide, hexane, toluene and mixtures thereof.

14. The process according to claim 5, wherein rabeprazole magnesium precipitates out spontaneously from the solvent.

15. A process for preparing rabeprazole magnesium, which comprises reacting rabeprazole freebase with magnesium alkoxide in an alcohol as solvent to form rabeprazole magnesium.

16. The process according to claim 15, wherein magnesium alkoxide is generated in situ by refluxing magnesium metal in the corresponding alcohol.

17. The process according to claim 15, wherein magnesium alkoxide is selected from the group consisting of magnesium methoxide, magnesium ethoxide, magnesium propoxide and magnesium isopropoxide.

18. The process according to claim 15, wherein the alcohol is selected from the group consisting of methanol, ethanol, propanol and isopropanol.

19. The process according to claim 5 or 15, wherein rabeprazole hemimagnesium is formed.

20. The process according to claim 5, 15 or 19, wherein the hydrate of rabeprazole magnesium is obtained.

21. The process according to claim 5, 15 or 19, wherein amorphous form of rabeprazole magnesium is obtained.

22. A method for treating or preventing gastrointestinal ulcers, which comprises administering to a patient in need thereof an effective amount of rabeprazole magnesium.

23. The method according to claim 22, wherein rabeprazole magnesium is used for healing of erosive or ulcerative gastroesophageal reflux disease (GERD); maintenance of healing of erosive or ulcerative GERD; healing of duodenal ulcer; or treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

24. The method according to claim 22, or 23 wherein rabeprazole hemimagnesium is administered.

25. A pharmaceutical composition for use in the treatment or prevention of gastrointestinal ulcers comprising an effective amount of rabeprazole magnesium and pharmaceutically acceptable excipients.

26. The pharmaceutical composition according to claim 25, wherein rabeprazole hemimagnesium is used.

27. The pharmaceutical composition according to claim 25, or 26 wherein a hydrate of the rabeprazole magnesium is used.

28. The pharmaceutical composition according to claim 25, or 26 wherein amorphous form of the rabeprazole magnesium is used.

29. The process for the preparation of rabeprazole magnesium as herein described and illustrated by the examples herein.

Dated this 6th day of **January, 2003.**

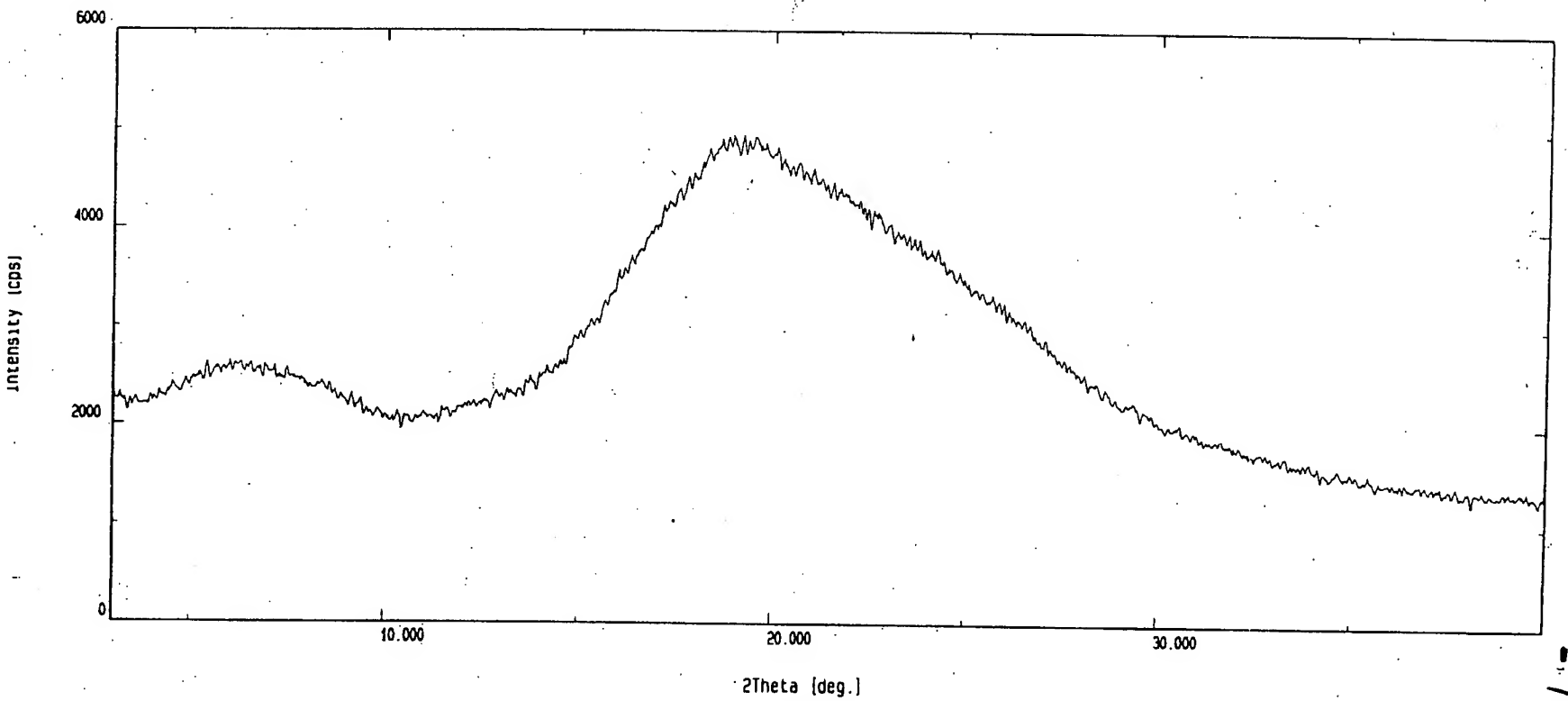
For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

ABSTRACT

The present invention relates to a novel magnesium salt of rabeprazole, to processes for preparing it, pharmaceutical compositions of the salt and to its use in treatment or prevention of gastrointestinal ulcers.

FIGURE I



For Ranbaxy Laboratories Limited

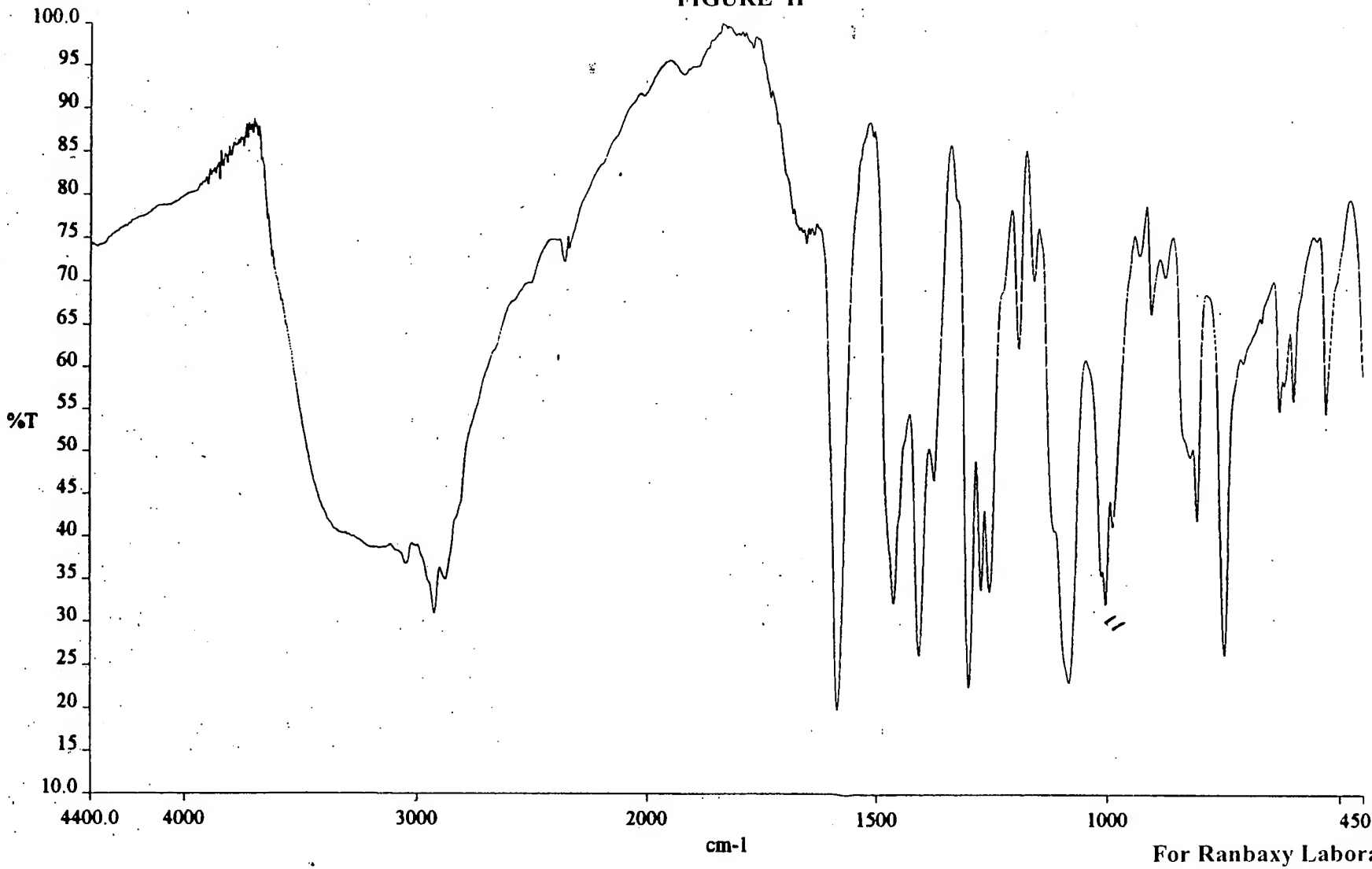
(Sushil Kumar Patawari)
Company Secretary

DUPLICATE

Ranbaxy Laboratories Limited

Application No.

FIGURE II

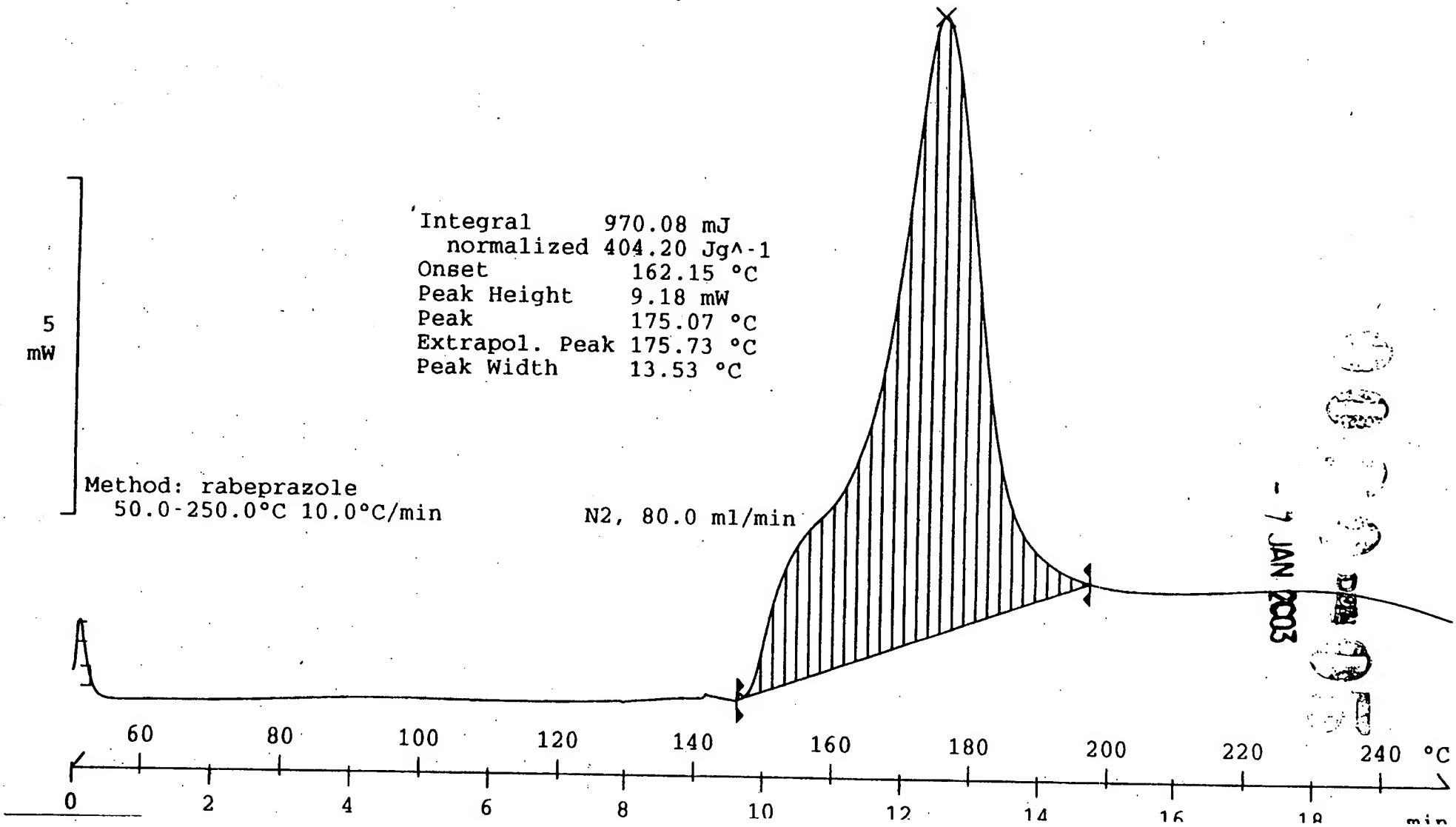


- 7 JAN 2003

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

FIGURE III



7 JAN 2003

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary